Synopsis

SYNOPSIS

The thesis entitled **"Studies towards the total synthesis of Psymberin, Hyptolide and Hypurticin"** is divided into three chapters.

CHAPTER I:

This chapter is further divided into two sections.

Section A:

This section deals with the introduction to 5,6-dihydropyran-2-ones and previous synthetic approaches of Hyptolide.

Section B:

This section describes the studies towards the total synthesis of Hyptolide and Hypurticin.

CHAPTER II:

This chapter deals with the introduction and earlier synthetic approaches of Psymberin.

CHAPTER III:

This chapter describes the studies directed towards the total synthesis of Psymberin.

CHAPTER I:

Section A: Introduction to 5,6-Dihydropyranones (α,β-unsaturated δ-lactones):

Lactone rings are a structural feature of many natural products. Of the naturally occurring lactones, which display a wide range of pharmacological activities, those bearing a 5,6-dihydropyran-2-one moiety are relatively common in various types of natural sources. Because of their manifold biological properties, these compounds are of marked interest not only from a chemical, but also from a pharmacological perspective. As a matter of fact, 5,6-dihydropyran-2-ones of both natural and non-natural origin have been found to be cytotoxic. In addition, they inhibit HIV protease, induce apoptosis, and have even proven to be antileukemic along with many other relevant pharmacological properties. At least some of these pharmacological effects may be related to the presence of the conjugated double bond, which acts as a Michael acceptor.

This section describes in brief introduction to 5,6-dihydropyranones (α,β-unsaturated δ-lactones) and their significance in the natural products and also describes the introduction and previous synthetic approaches of hyptolide, a potent cytotoxic agent.

Section B: Studies directed towards the total synthesis of Hyptolide and Hypurticin:

PRESENT WORK AND DISCUSSION:

HYPTOLIDE 1:

Lactone ring constitute a structural feature of a broad range of natural products. Many of these lactones, most particularly those being α,β-unsaturated, display pharmacologically relevant properties (e.g. antitumoral or tumor-promoting activity). Among them the conjugated δ-lactone (+)-hyptolide **1** have been isolated from the leaves of *Hyptis pectinata* species of the family *Lamiaceae*. This compound contains a polyoxygenated chain connected with an α,β-unsaturated six membered δ-lactone and shows cytotoxicity against human tumor cell lines (Figure 1).

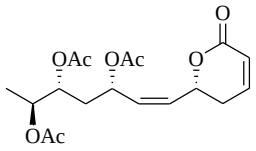


Figure 1. Hyptolide 1

HYPURTICIN 2:

Hypurticin **2** is a highly flexible polyacyloxy-6-heptenyl-5,6-dihydro-2*H*-pyran-2-one isolated from *Hyptis urticoides* by Romo de Vivar's group. The structural reassignment, absolute configuration and conformational behavior of highly flexible natural product hypurticin were ascertained by a molecular modeling protocol, which includes extensive conformational searching, geometry optimization ^{1}H-^{1}H NMR coupling constants. The structure of hypurticin was found to be 6*S*-[3′*S*,5′*R*,6′*S*-triacetoxy-1*Z*-heptenyl]-5*S*-acetoxy-5,6-dihydro-2*H*-pyran-2-one (Figure 2).

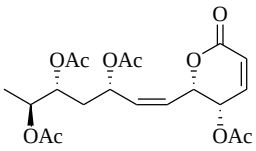
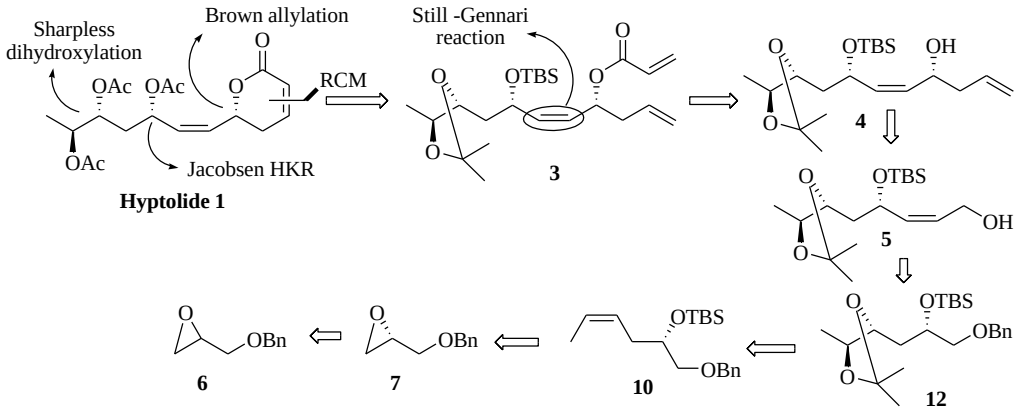


Figure 2. Hypurticin 2

Retrosynthetic analysis of Hyptolide 1:

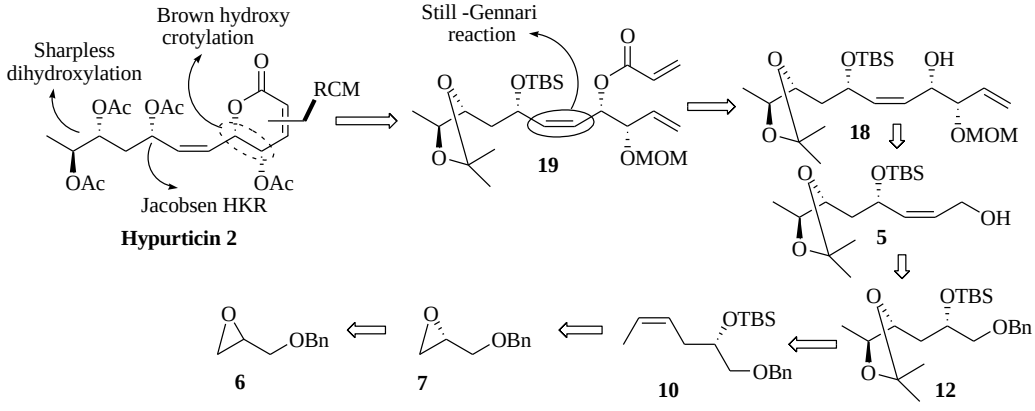
As depicted in Scheme 1, retrosynthetically hyptolide **1** was envisioned to be obtained by the ring closing metathesis of acrylate **3**. Intermediate **4** was in turn obtained from the Brown asymmetric allylation of *Z*-alkenal derived from **5**. The alcohol **5** in turn obtained by the series of reactions involving Still-Gennari olefination, Sharpless asymmetric dihydroxylation and Jacobsen kinetic resolution as key reactions starting from benzyl glycidyl ether **6**.



Scheme 1. Retrosynthetic analysis of hyptolide.

Retrosynthetic analysis of Hypurticin 2:

Retrosynthetic analysis revealed that hypurticin **2** can be obtained by the ring closing metathesis of acrylate **19**, which in turn obtained by the diastereo and enantioselective hydroxy crotylation of *Z*-alkenal derived from **5**.

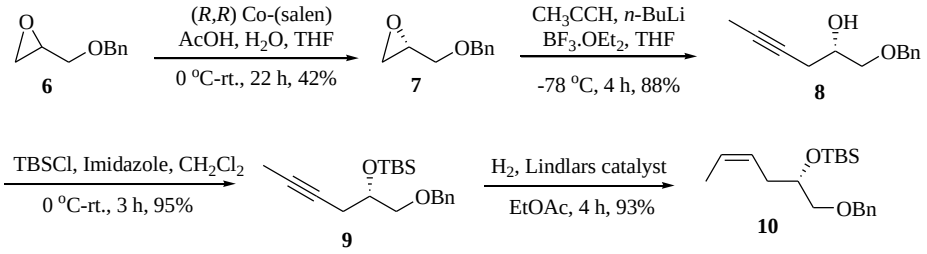


Scheme 2. Retrosynthetic analysis of hypurticin.

The alcohol **5** in turn obtained by the series of reactions involving Still-Gennari olefination, Sharpless asymmetric dihydroxylation and Jacobsen kinetic resolution as key reactions starting from benzyl glycidyl ether **6** (Scheme 2).

RESULTS AND DISCUSSION:

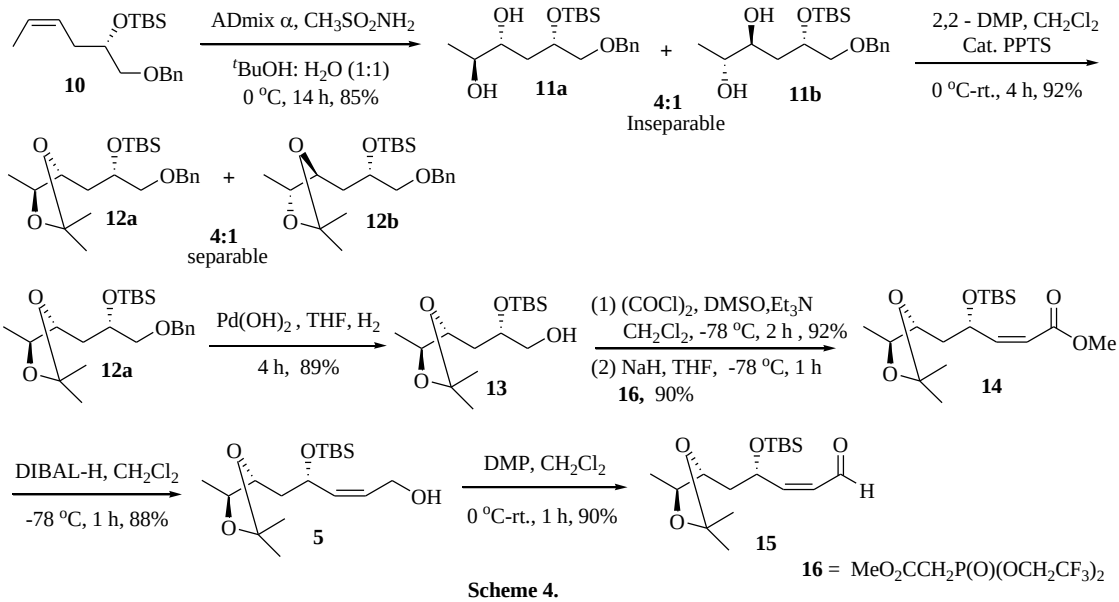
The reaction sequence showed in Scheme 3, describes the synthesis of hyptolide **1** and hypurticin **2**. Synthesis commenced from (*S*)-benzyl glycidyl ether **7**. The Jacobsen resolution of benzyl glycidyl ether **6** using (*R*,*R*)-(salen)cobalt(II) precatalyst, acetic acid (AcOH) and H_2O (0.55 equiv) for 22 h resulted in (*S*)-benzyl glycidyl ether **7** in 42% yield. Regioselective opening of the epoxide **7** with propynyllithium, formed on treatment of condensed propyne gas with *n*-BuLi, in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in THF at -78 ^oC resulted in homopropargyl alcohol **8** in 88% yield, which was protected as TBS ether using TBDMSCl and imidazole in CH_2Cl_2 at 0 ^oC to room temperature furnished TBS ether **9** in 95% yield. Partial hydrogenation of triple bond under Lindlar's conditions (H_2-Pd/$CaCO_3$) in EtOAc afforded the *Z*-olefin **10** in 93% yield.



Scheme 3.

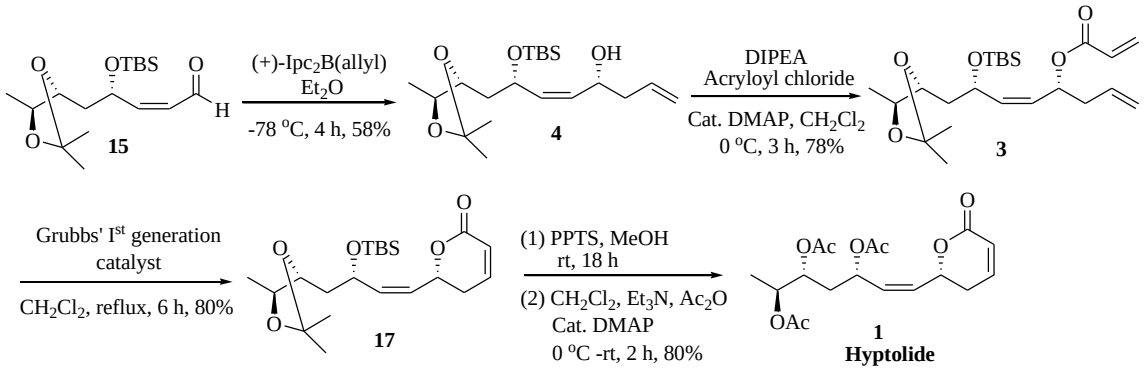
The *Z*-olefin **10** was subjected to Sharpless asymmetric dihydroxylation protocol by using the combination ADmix-α and methane sulfonamide in ^tBuOH:H_2O (1:1) afforded the diol **11a** and **11b** as a inseparable diastereomeric mixture in 4:1 ratio. The diol **11a** and **11b** upon treating with 2,2-dimethoxy propane in CH_2Cl_2 using catalytic PPTS at 0 ^oC afforded the acetonide protected compound **12a** and **12b** as a separable diastereomeric mixture in 4:1 ratio in 92% yield, cleavage of the benzyl ether **12a** using $Pd(OH)_2$ afforded the primary alcohol **13** in 89% yield. The primary alcohol **13** was oxidized under Swern oxidation conditions at -78 ^oC to afford the corresponding aldehyde, which was subjected

to a Still-Gennari reaction in presence of NaH in THF to provide the α,β-unsaturated ester compound **14** in 90% yield. The chemoselective reduction of α,β-unsaturated ester **14** with DIBAL-H at -78 ^{o}C in CH_2Cl_2 afforded the allyl alcohol **5** in 95% yield. The allyl alcohol **5** was oxidized to its corresponding aldehyde **15** by treating with Dess-Martin Periodinane in dry CH_2Cl_2, which was used for next reaction without further purification (Scheme 4).



Scheme 4.

As depicted in Scheme 5, aldehyde **15** was subjected to asymmetric allylation following Brown's protocol by using (+)-β-allyldiisopinocampheylborane solution (1 M in Pentane) to afford the secondary alcohol **4.** Acylation of **4** with acryloyl chloride in the presence of Hünig's base furnished acrylate **3**.



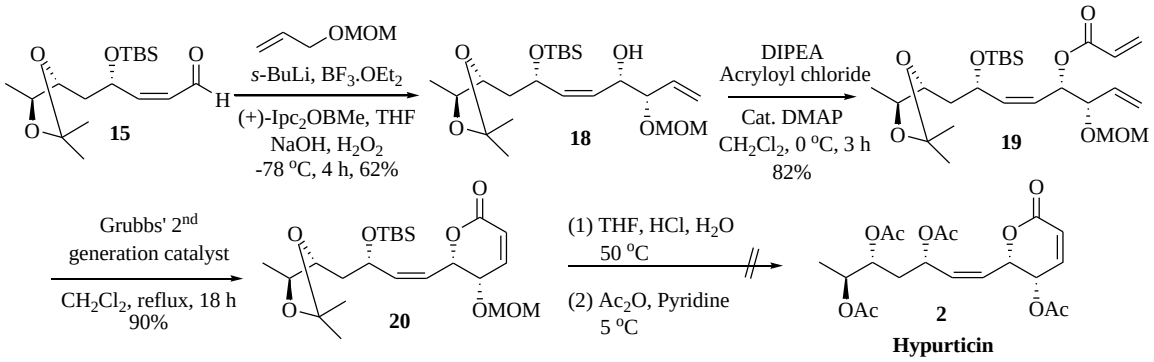
Scheme 5.

Acrylate **3** was subjected to ring closing metathesis using Grubbs' 1st generation catalyst to afford the α,β-unsaturated δ-lactone **17** in 80% yield, which was converted to

hyptolide **1** in two steps-global deprotection by using PPTS in MeOH at room temperature, followed by acetylation of the resulting triol with acetic anhydride, triethylamine and catalytic DMAP in CH_2Cl_2 at 0 ^oC afforded hyptolide **1** in 80% yield (Scheme 5). The spectral and analytical data of **1** were in good agreement with those reported in the literature.

The treatment of aldehyde **15** with *in situ* generated [(*Z*)-γ-(Methoxymethoxy)allyl]-diisopinocampheylborane, [prepared from methoxy-methyl allyl ether, *s*-BuLi, Ipc_2-BOMe (derived from (+)-*α*-pinene) and $BF_3{\cdot}OEt_2$] in THF at -78 ^oC to 25 ^oC in a regioselective and stereoselective manner yielded the corresponding *threo*-β-methoxymethyl homoallyl alcohol **18** with ≥ 99% diastereoselectivity and > 95% enantioselectivity in 62% yield (Scheme 6).

The protection of the secondary alcohol was achieved with acryloyl chloride in the presence of Hünig's base to afford compound **19** in 82% yields. The crucial ring closing metathesis of the compound **19** was achieved with Grubbs' 2nd generation catalyst in CH_2Cl_2 at reflux condition to afford the required 5,6-dihydro-2*H*-pyran-2-one **20** in 90% yield. Unfortunately, the deprotection of acetonide, TBS ether and MOM ether groups of compound **20** gave no desired product on exposure to the various acidic conditions (Scheme 6).



Scheme 6.

In conclusion, we have synthesized hyptolide **1** by using Jacobsen's hydrolytic kinetic resolution, Sharpless asymmetric dihydroxylation, Brown's asymmetric allylation

and Grubbs' ring closing metathesis as key reactions. Further trails are in progress for the total synthesis of hypurticin **2**.

CHAPTER II:

Natural products continue to be excellent sources for new drug molecules, especially in the area of anticancer therapeutics. In several instances, the minute quantities of the material typically isolated from natural source restrict the ability of research groups to investigate the lead compounds. The natural sources like plants, terrestrial micro organism and marine organisms (sponges, tunicates and shell less mollusks) have been in the focus for the search of new drug candidate. Especially those from marine origin are often obtained in minute quantities, which is insufficient for extensive *in vitro* studies, determination of structure-activity relationship (SAR) and *in vivo* studies. Organic synthesis can facilitate the preparation of sufficient amounts of such compounds and even create the simplified analogs of the target compound which can be of same or more biological activity.

This chapter describes in brief the marine natural products and their significance as anticancer primary leads and also describes the introduction and previous synthetic approaches to psymberin, which is a highly potent cytotoxic agent.

CHAPTER III:

This chapter describes our studies directed towards the total synthesis of psymberin a potent cytotoxic agent.

In 2004, two groups led by Pettit and Crews independently disclosed the isolation of constitutionally identical cytotoxins, irciniastatin A and psymberin from the marine sponges *Ircinia ramose* and *Psammocinia* sp., respectively. From the outset, irciniastatin A and psymberin appeared to be constitutionally equivalent based on high resolution mass spectrometry, in conjunction with the 1D and 2D NMR data. The absolute configuration of psymberin was assigned by the Crews group based on combination of CD and other spectroscopic studies. Importantly, both isolates displayed significant cancer cell growth inhibitory activity against a wide variety of human cancer cell lines. The DeBrabander group announced the first total synthesis of (+)-psymberin, which not only established the

structural assignment, including absolute configuration, but also confirmed that (+)-irciniastatin A and (+)-psymberin **21** were in fact one and the same (Figure 3).

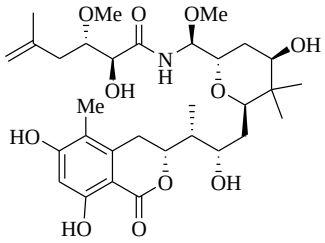
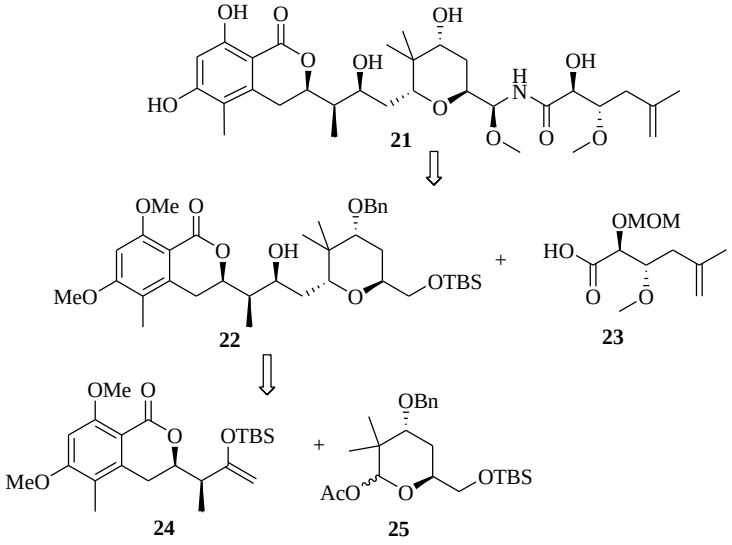


Figure 3. Psymberin 21

Structurally psymberin **21** consists of an aromatic part i.e., dihydroisocoumarin unit, dimethyl tetrahydropyran ring, *N*-acyl aminal group and acyclic psymberic acid side chain.

Because of the scarcity from natural source and high importance in terms of its cytotoxicity, psymberin attracted the attention of several synthetic organic chemists towards its synthesis which resulted in its total syntheses, some analogues and its intermediates syntheses. Our efforts *en route* to the synthesis of psymberin, we report herein the studies directed towards its total synthesis.

RETROSYNTHETIC ANALYSIS OF PSYMBERIN (21):



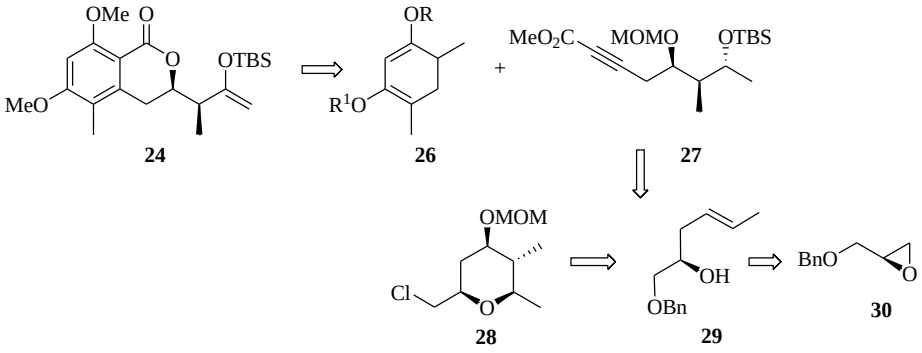
Scheme 7. Retrosynthetic analysis of psymberin 21

Retrosynthetically, psymberin **21** was envisioned to be obtained by the late stage attachment of psymberic acid side chain by coupling of acid chloride derived from the **23** with the hemiaminal derived from **22**. Compound **22** was synthesized by Lewis acid mediated Mukaiyama aldol reaction of enolsilane **24** with dimethyl tetrahydropyran acetate **25** (Scheme 7).

Structurally psymberin **21** consists of three major units i.e., dihydroisocoumarin unit **24**, dimethyl tetrahydropyran ring **25** and acyclic psymberic acid side chain **23**.

Synthesis of dihydroisocoumarin unit 24:

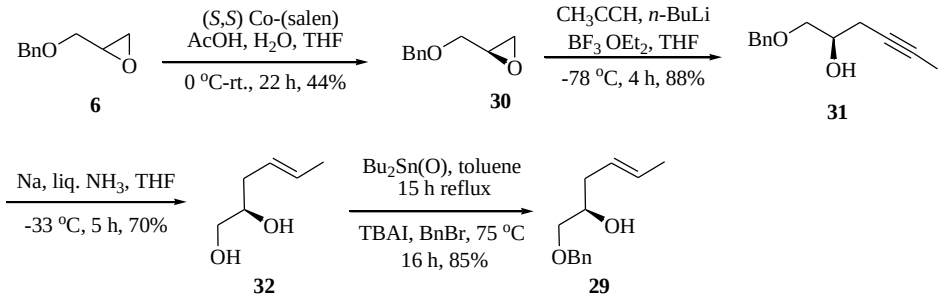
Retrosynthetic strategy for dihydroisocoumarin fragment **24** of psymberin **21** was depicted in Scheme 8. It has been envisaged that fragment **24** can be prepared by the *Diels Alder* reaction of diene **26** with the dienophile **27**. The dienophile **27** is obtained by the reductive opening of chloromethyl tetrahydropyran **28** by some functional group modifications. Compound **28** in turn is obtained from the Prins cyclization of homoallylalcohol **29** with acetaldehyde. The homoallylic alcohol **29** with its single stereogenic center could be easily synthesized from (*R*)-benzyl glycidyl ether **30.**



Scheme 8. Retrosynthestic analysis of dihyroisocoumarin unit 24

As depicted in Scheme 9**,** synthesis commenced from (*R*)-benzyl glycidyl ether **30**. The Jacobsen resolution of benzyl glycidyl ether **6** using (*S*,*S*)-(salen)cobalt(II) precatalyst, acetic acid (AcOH) and H_2O (0.55 equiv) for 22 hours resulted in (*R*)-benzyl glycidyl ether **30** in 44% yield. Regioselective opening of the epoxide **30** with propynyllithium, formed on treatment of condensed propyne gas with *n*-BuLi, in the presence of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in THF at -78 ^oC resulted in homopropargyl alcohol **31** in 88% yield. Birch reduction of **31** using Na in liquid NH_3 furnished dihydroxy *trans* olefin **32** in

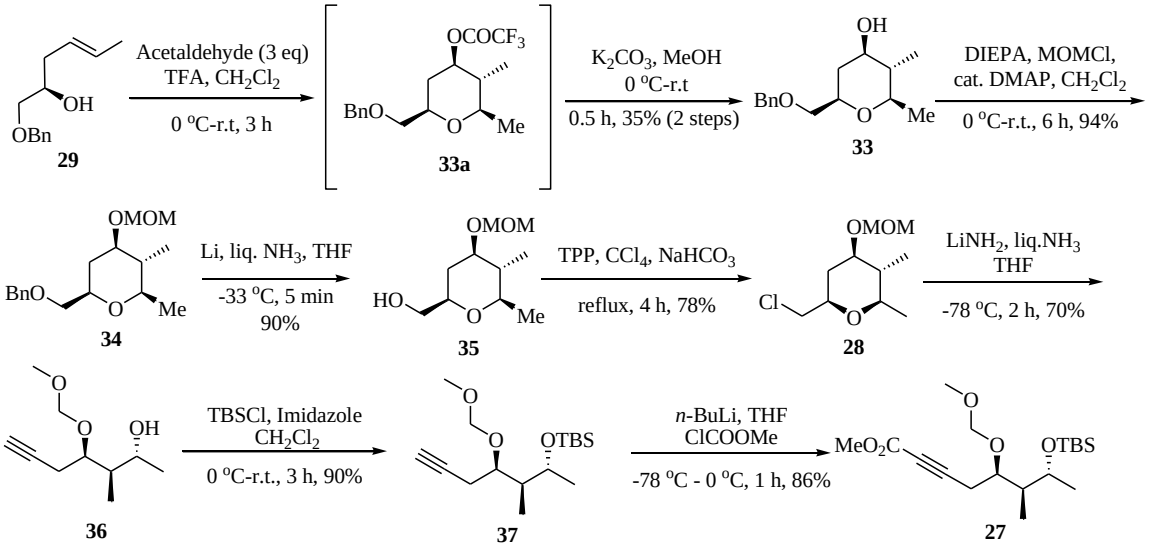
70% yield. Then, selective protection of the primary hydroxyl group as benzyl ether in presence of $Bu_2Sn(O)$, TBAI and BnBr in toluene reflux for 15 hours afforded homoallylic alcohol **29** in 85% yield.



6 **30** **31** **32** **29**

Scheme 9.

Homoallylic alcohol **29** subjected to crucial Prins cyclization with acetaldehyde using trifluoroacetic acid (TFA) in CH_2Cl_2 followed by hydrolysis of resulting trifluoroacetate **33a** using potassium carbonate (K_2CO_3) in methanol afforded tetra substituted pyran **33** in 35% yield. The secondary alcohol of tetrahydropyran **33** was protected as methoxymethylether (MOM ether) using MOMCl in presence of diisopropylethylamine and a catalytic DMAP in CH_2Cl_2 at 0 °C to room temperature to provide MOM ether **34** in 94% yield. Compound **34** on benzyl ether deprotection with Li in liquid ammonia in THF resulted in primary alcohol **35** in 90% yields.

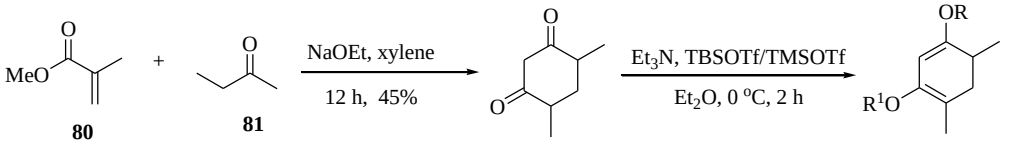


29 **33a** **33** **34** **35** **28** **36** **37** **27**

Scheme 10.

The primary alcohol **35** was treated with TPP, CCl_4 and $NaHCO_3$ under reflux conditions to furnish corresponding chloromethyl tetrahydropyran **28** in 78% yield. Reductive-elimination of chloromethyl pyran system **28** with $LiNH_2$ in liquid NH_3 following our group well established protocol, resulted in 1,3-antidiol motif **36** in 70% yield. Protection of secondary hydroxyl group as TBS ether by using TBS chloride and imidazole in CH_2Cl_2 furnished TBS protected alcohol **37** in 90% yield. The alkyne **37** was lithiated with *n*-BuLi in THF and then treated with methylchloroformate at -78 ^oC to afford substituted propargylic ester **27** in 86% yield (Scheme 10).

As depicted in Scheme 11, the diene **26** was prepared from 4,6-Dimethyl-1,3-cyclohexadienone **79**, which in turn prepared from methylmethacrylate **80** and 2-butanone **81** in presence of sodium ethoxide in xylene. 4,6-Dimethyl-1,3-cyclohexadienone **79** converted to diene **26** upon treatment with Et_3N and TBSOTf or TMSOTf in Et_2O at 0 ^oC, which was used directly for the *Diels Alder* reaction without further purification.



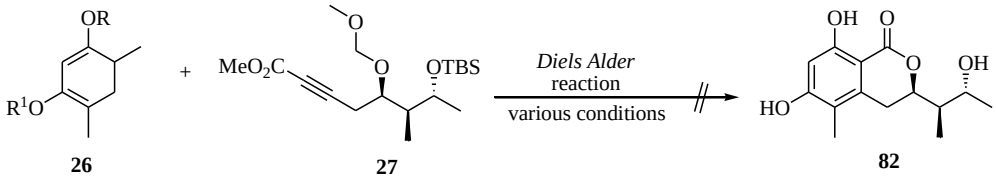
80 **81** **79** **26**

R = TMS, TBS

R^1 = TMS, TBS

Scheme 11.

As our initial efforts to standardize the *Diels Alder* reaction between different dienes **26** and dienophile **27** under various conditions were unsuccessful (Scheme 12). We were forced to revise the synthetic strategy for the synthesis of fragment **24**.



26 **27** **82**

R = TBS, TMS

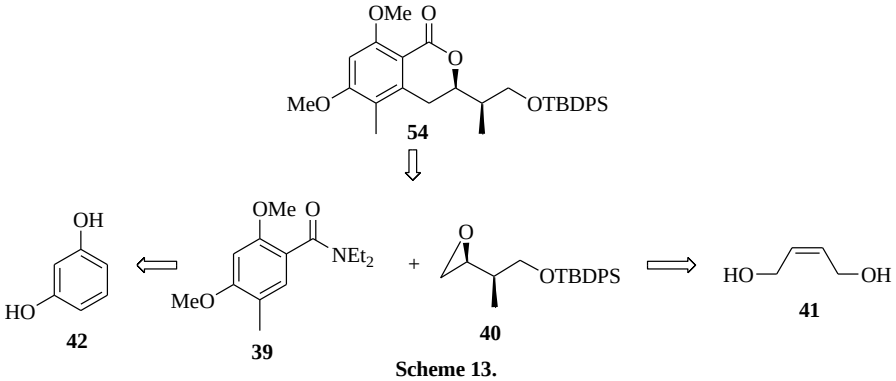
R^1 = TBS, TMS

no reaction

Scheme 12.

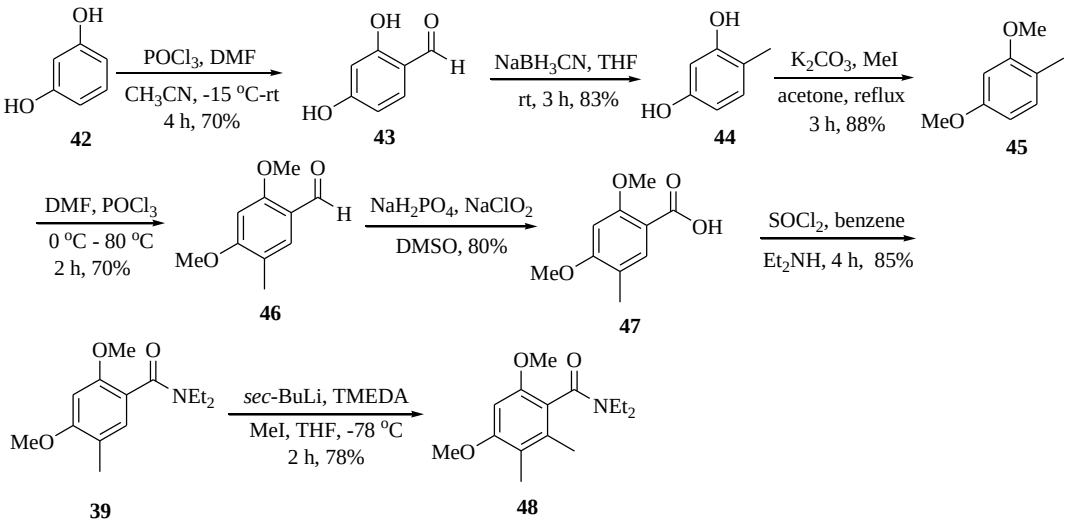
Revised retrosynthetic strategy for fragment 54:

Revised retrosynthetic strategy for dihydroisocoumarin unit **54** of psymberin **21** is depicted in Scheme 13. It has been envisaged that regioselective opening of epoxide **40** with an amide **39** followed by subsequent reactions will provide dihydroisocoumarin unit **24**. The epoxide **40** in turn obtained from *cis*-2-butane-1,4-diol **41**. Amide **39** obtained from resorcinol **42** by involving a series of reactions.



Scheme 13.

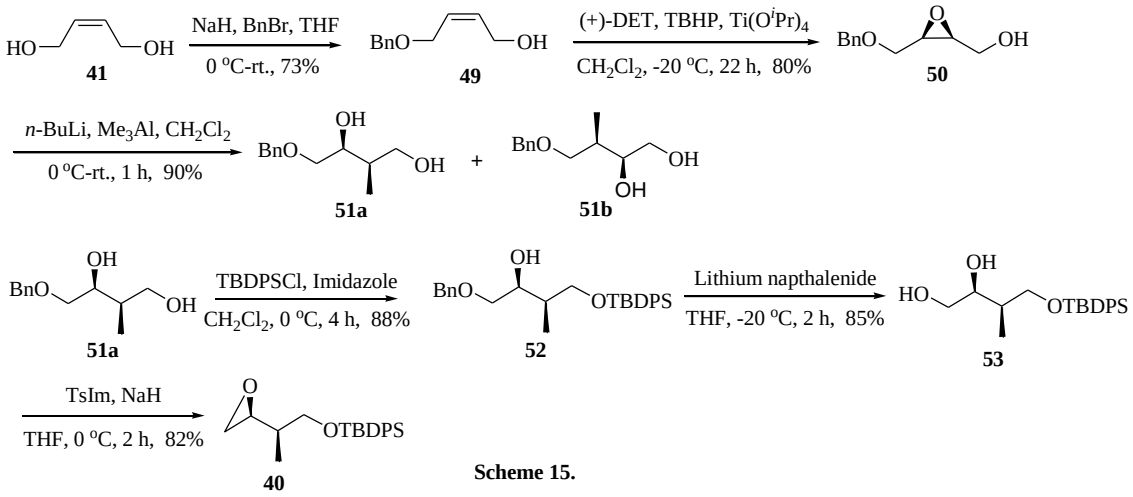
The synthesis of aromatic fragment began with the Vilsmeier formylation of resorcinol **42** with $POCl_3$ and DMF in acetonitrile yielded 2,4-dihydroxy benzaldehyde **43** in 70% yield**,** which on subsequent reduction with sodium cyanoborohydride in THF gave dihydroxy toluene **44** in 83% yield. Protection of hydroxyl groups as methyl ethers using potassium carbonate and methyl iodide in acetone afforded 2,4-dimethoxy toluene **45** in 88% yield.



Scheme 14.

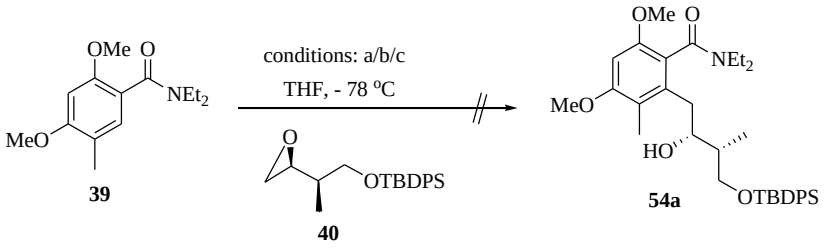
Vilsmeier formylation of **45** gave aldehyde **46**, which on subsequent oxidation with NaH_2PO_4 and $NaClO_2$ in DMSO gave acid **47** in 80% yield. Amidation of acid **47** by treating with thionyl chloride in benzene followed by addition of diethyl amine yielded *N*,*N'*-diethyl-2,4-dimethoxy-5-methylbenzamide **39** in 85% yield. Lithiation of amide **39** with *sec*-BuLi and TMEDA in THF at -78 ^oC followed by addition of methyl iodide afforded methylated amide **48** in 78% yield (Scheme 14).

Synthesis of epoxide **40** begun with commercially available *cis*-butene-1,4-diol **41**, which was protected as its mono benzyl ether in THF at room temperature to yield **49** in 73% yield. The allylic alcohol **49** was subjected to Sharpless asymmetric epoxidation using L-(+)-DET, $Ti(O^iPr)_4$ and TBHP at -20 ^oC in CH_2Cl_2 to furnish the chiral epoxy alcohol **50** in 80% isolated yield. The regioselective opening of chiral epoxy alcohol **50** with *n*-BuLi and trimethyl aluminium (Me_3Al) in CH_2Cl_2 at 0 ^oC to room temperature afforded a mixture of 1,3-diol **51a** and 1,2-diol **51b** in 92:8 ratio in 90% yield. Selective protection of primary alcohol **51a** with TBDPSCl and imidazole in CH_2Cl_2 gave TBDPS ether **52** in 88% yield. Deprotection of benzyl ether using Li-naphthalenide in THF at -20 ^oC afforded diol **53** in 85% yield. The 1,2-diol was converted to oxirane by treatment with NaH and tosylimidazole in THF at 0 ^oC to room temperature to yield epoxide **40** in 82% yield (Scheme 15).



Scheme 15.

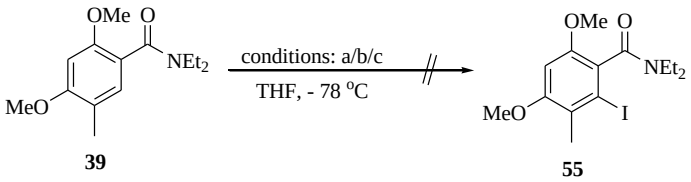
Initially we thought that lithiation of tertiary amide **39** with *sec*-BuLi or *t*-BuLi followed by the addition of epoxide **40** in presence of boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) or TMEDA in THF at -78 ^oC under various conditions will provide aromatic core **54a**, but efforts were unsuccessful (Scheme 16).



conditions : a = *s*-BuLi, TMEDA., b = *s*-BuLi, BF_3OEt_2., c = *t* -BuLi, BF_3OEt_2

Scheme 16.

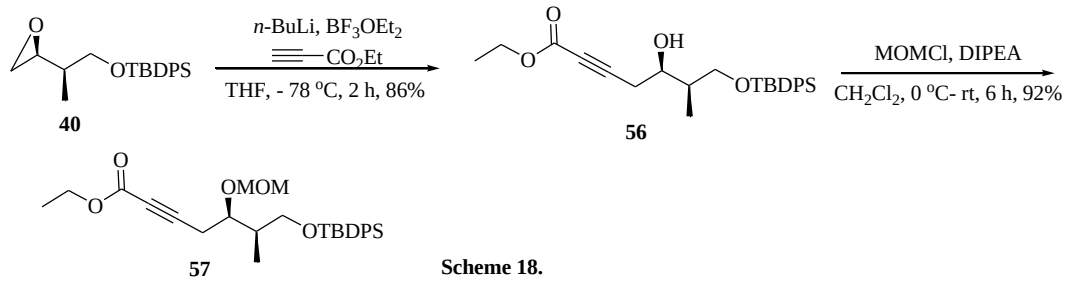
Then we thought that aromatic core can be achieved by the *ortho*-metallation of tertiary amide **39**, followed by the regioselective opening of epoxide **40** with lithium exchange of *ortho*-metallated tertiary amide **55** but the *ortho*-metallation of tertiary amide under various experimental conditions were unsuccessful (Scheme 17).



conditions : a =*s*-BuLi, TMEDA, I_2; b=*s*-BuLi, TMEDA, ICl; c=*t*-BuLi, ICl

Scheme 17.

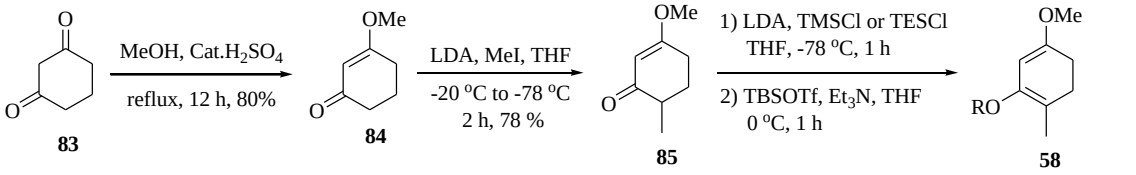
Regioselective opening of epoxide **40** with ethylpropiolate in presence of *n*-BuLi and boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) in THF at -78 ^oC afforded substituted propargylic ester **56** in 86% yield. Protection of secondary alcohol **56** as methoxymethylether (MOM ether) using MOMCl in presence of diisopropylethylamine in CH_2Cl_2 at 0 ^oC to room temperature provided MOM ether **57** in 92% yield (Scheme 18).



40 **56** **57**

Scheme 18.

The diene **58** was prepared from 1,3-cyclohexadienone **83**. The 1,3-cyclohexadienone **83** was converted into 3-methoxy-2-cyclohexenone **84** upon treatment with catalytic amount of H_2SO_4 in anhydrous methanol, which was further alkylated at 6th position using lithium diisopropylamide and iodomethane, yielding 3-methoxy-6-methyl-2-cyclohexenone **85**. Methylated enone **85** was converted to diene **58** upon treatment with LDA and TMSCl/TESCl or Et_3N and TBSOTf in THF, which was used directly for the *Diels Alder* reaction without further purification (Scheme 19).



83 **84** **85** **58**

Scheme 19.

R = TMS, TBS, TES

Efforts to standardize the *Diels Alder* reaction between different dienes **58** and dienophile **57** under various conditions were unsuccessful (Scheme 20).

58 **57** **59**

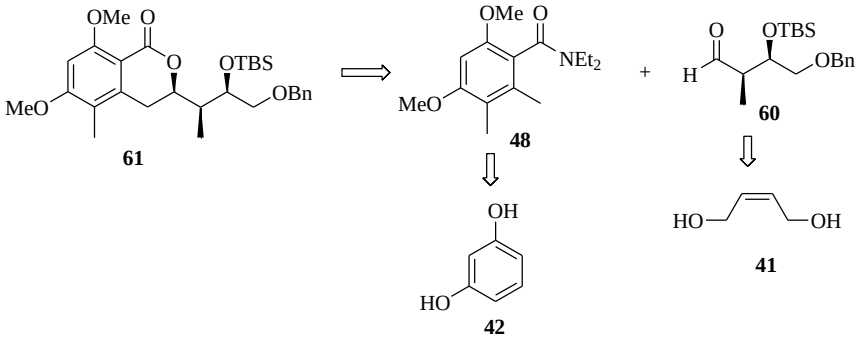
R = TMS,TES or TBS

Scheme 20.

Above results forced us to re revise the synthetic strategy for the synthesis of aromatic fragment**.**

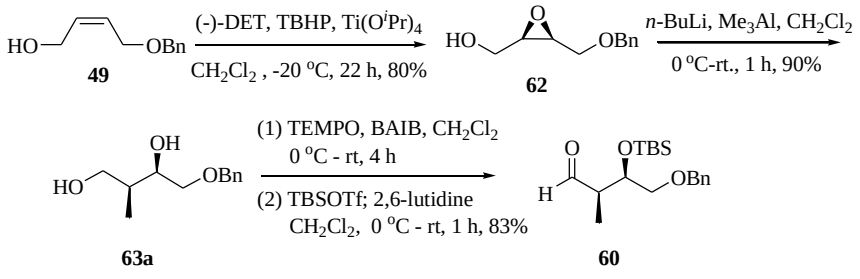
Re revised retrosynthetic strategy for fragment 61:

Re revised retrosynthetic strategy for dihydroisocoumarin unit **61** of psymberin **21** is depicted in Scheme 21. It has been envisaged that the anion derived from amide **48** will be added smoothly onto the aldehyde **60**, which on further sequence of reactions will afford dihydroisocoumarin unit. The aldehyde **60** in turn obtained from *cis*-2-butane-1,4-diol **41**. Amide **48** obtained from resorcinol **42** by involving a series of reactions.



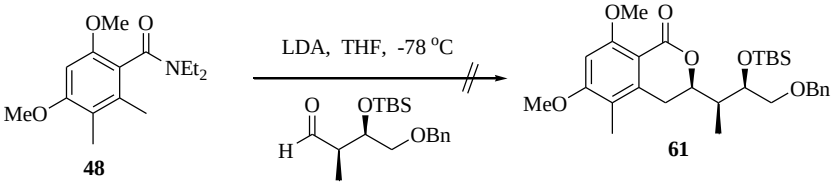
Scheme 21.

As depicted in Scheme 22, synthesis of aldehyde **60** began with the mono protected benzyl ether **49**, which was subjected to Sharpless asymmetric epoxidation by using D-(-)-DET, $Ti(O^iPr)_4$ and TBHP at -20 ^oC in CH_2Cl_2 to furnish the chiral epoxy alcohol **62** in 80% isolated yield. The regioselective opening of chiral epoxy alcohol **62** with *n*-BuLi and trimethyl aluminium (Me_3Al) in CH_2Cl_2 at 0 ^oC to room temperature afforded a mixture of 1,3-diol **63a** and 1,2-diol **63b** in 92:8 ratio in 90% yield. Selective oxidation of primary alcohol **63a** with TEMPO and BAIB in CH_2Cl_2 at 0 ^oC to room temperature afforded corresponding aldehyde, which was protected as TBS ether using TBSOTf and 2,6 -lutidine in CH_2Cl_2 at 0 ^oC to give the TBS protected aldehyde **60**.



Scheme 22.

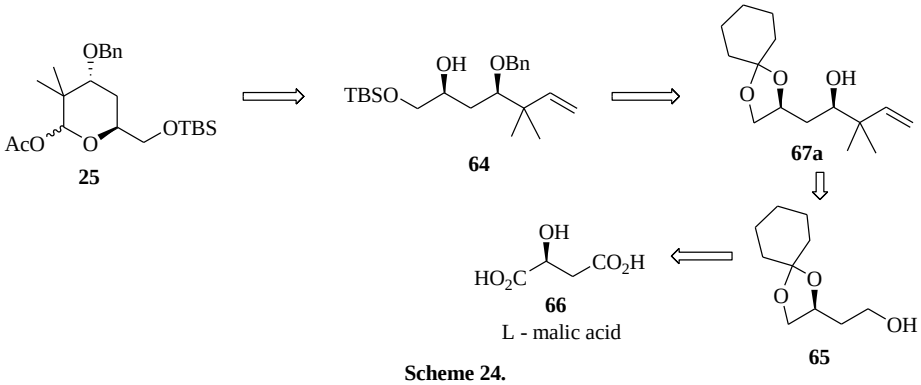
Initially we thought that the anion derived from amide **48** with LDA in THF at -78 ^{o}C, followed by the addition of aldehyde **60** will afford the adduct **61** (Scheme 23), but the efforts were unsuccessful.



Scheme 23.

Synthesis of dimethyl tetrahydropyran ring 25:

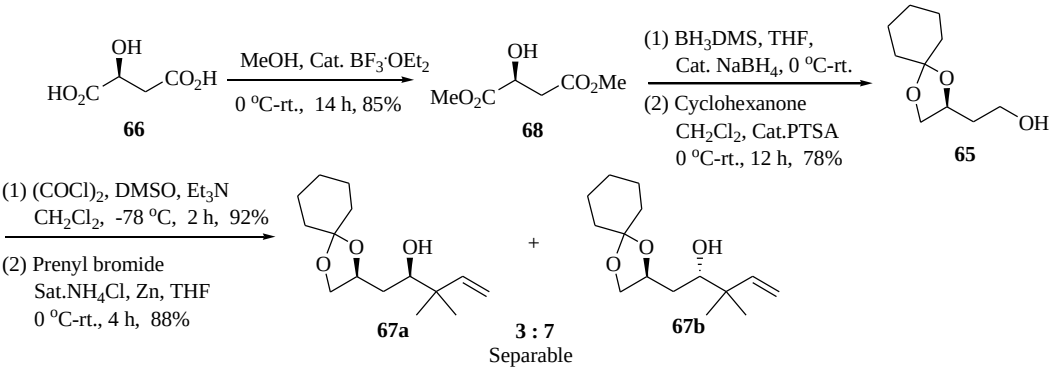
As depicted in Scheme 24, retrosynthetically dimethyl tetrahydropyran ring **25** was envisioned to be obtained by the ozonolytic cleavage of terminal alkene of **64,** followed by trapping as acetate **25**, which in turn obtained by the sequence of reaction involving Barbier type allylation, oxidation and *syn*-stereoselcetive reduction starting from known alcohol **65** derived from L-malic acid **66**.



Scheme 24.

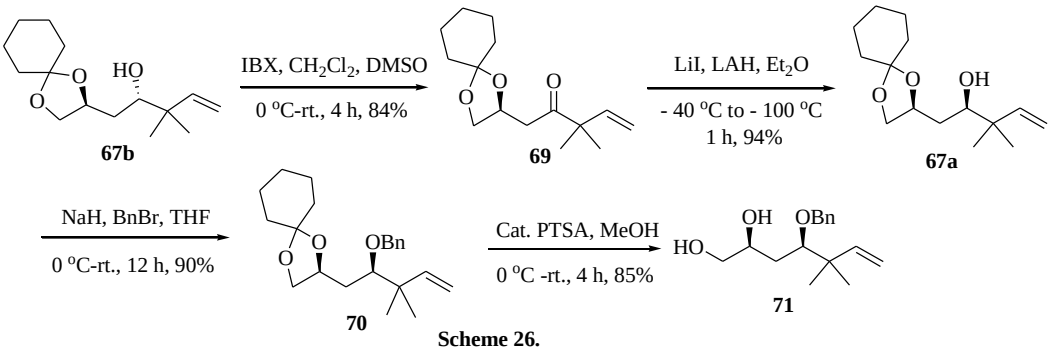
As shown in Scheme 25, synthesis began with L-malic acid **66**. Malic acid was converted into malic acid dimethyl ester **68** upon treatment with catalytic amount of $BF_3{\cdot}OEt_2$ in anhydrous methanol, which was reduced to (*S*)-1,2,4-butanetriol upon treatment with borane-dimethylsulfide ($BH_3{\cdot}Me_2S$) in presence of catalytic amount of $NaBH_4$ at 0 ^{o}C to room temperature. The triol was protected as 1,2-O-cyclohexylidene acetal using cyclohexanone and catalytic PTSA in anhydrous CH_2Cl_2 to yield cyclohexylidene acetal **65** in 78% yield. Alcohol **65** subjected to Swern oxidation conditions to give the corresponding aldehyde, which on further treatment with Zn and 3,3-dimethyl ally bromide in THF-aqueous NH_4Cl at 0 ^{o}C to room temperature for 4 h,

under Barbier reaction conditions afforded carbinol **67a** and **67b** as a separable diastereomeric mixture (3:7 ratio) in 88% yield.



Scheme 25.

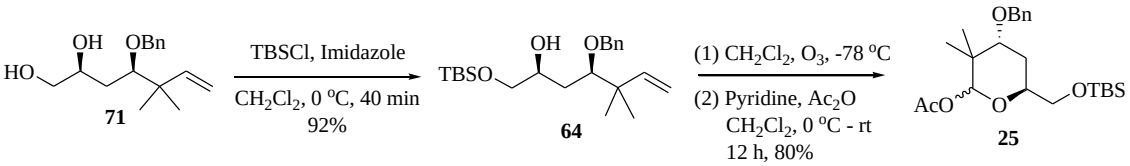
Oxidation of unrequired *anti* alcohol **67b** with IBX in DMSO and CH_2Cl_2 gave ketone **69,** which on highly *syn*-stereoselective 1,3-asymmetric reduction afforded the desired *syn*-diol **67a** in 94% yield (*syn*:*anti*=92:8) by using $LiAlH_4$-LiI in ether at -100 °C.



Scheme 26.

Protection of hydroxyl group as benzyl ether **70** using NaH and benzyl bromide in THF, followed by acid catalyzed cleavage of cyclohexylidene acetal **70** using catalytic PTSA in methanol at room temperature for 4 h afforded diol **71** in 85% yield (Scheme 26).

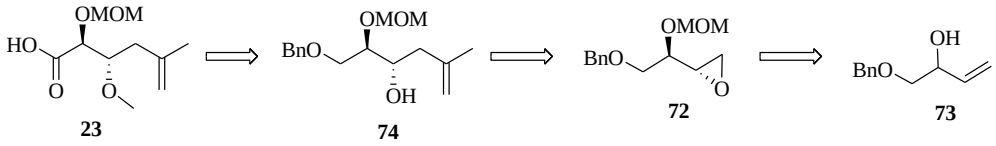
Selective protection of the primary hydroxyl group **71** as TBS ether using TBSCl and imidazole in CH_2Cl_2 at 0 °C provided TBS ether **64.** The terminal alkene **64** subjected to ozonolytic cleavage and the resulting lactol was trapped as acetate using pyridine and acetic anhydride to provide dimethyl tetrahydropyran **25** in 80% yield (Scheme 27).



Scheme 27.

Synthesis of psymberic acid side chain fragment 23:

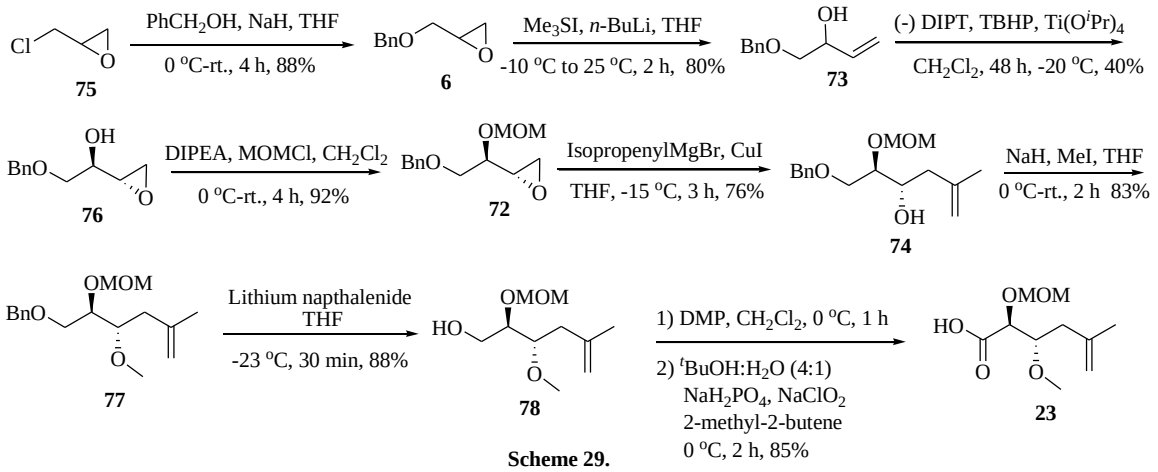
As depicted in Scheme 28, retrosynthetically psymberic acid side chain **23** was envisioned to be obtained by the regioselective opening of epoxide **72** with isopropenyl magnesium bromide followed by subsequent reactions, the epoxide **72** in turn obtainable by the Sharpless asymmetric resolution of allylic alcohol **73**.



Scheme 28.

The reaction sequence shown in Scheme 29, describes the synthesis of psymberic acid side chain **23**. Treatment of epichlorohydrin **75** with benzoxide formed by the treatment of benzyl alcohol with NaH in THF yielded benzylglycidyl ether **6** in 88% yield**.** Opening of epoxide with trimethylsulfonium iodide and *n*-Butyl lithium in THF at -8 ^{o}C furnished homologated allylic alcohol **73** in 80% yield. The allylic alcohol was subjected to Sharpless asymmetric kinetic resolution protocol using D-(-)-diisopropyl tartarate, Ti($O^{i}Pr$)$_4$ and TBHP in CH_2Cl_2 at -20 ^{o}C for 2 days afforded epoxyalcohol **76** in 40% yield. The secondary alcohol was protected as methoxymethyl ether using MOMCl in presence of diisopropylethylamine in CH_2Cl_2 at 0 ^{o}C to room temperature provided MOM ether **72** in 92% yield**.** Regioselective opening of epoxide **72** with isopropenyl magnesium bromide in presence of CuI at -15 ^{o}C in THF afforded the homoallylic alcohol **74** in 76% yield. Protection of hydroxyl group as methyl ether using NaH and MeI in THF at 0 ^{o}C to room temperature provided methyl ether **77** in 83% yield. Cleavage of benzyl ether by using Li-naphthalenide in THF at -23 ^{o}C afforded primary alcohol **78** in 88% yield. Oxidation of primary alcohol **78** using Dess Martin reagent in CH_2Cl_2 furnished aldehyde

which was further converted to acid using $NaClO_2$, NaH_2PO_4 and 2-methyl-2-butene in ^tBuOH and H_2O afforded acid[3] **23** in 85% yields.



Scheme 29.

In conclusion, we have synthesized three key building blocks i.e., aryl fragment **48**, dimethyl tetrahydropyran core **25** and psymberic acid side chain **23** for the total synthesis of psymberin. Coupling of these fragments to *en route* to the total synthesis of psymberin are in progress.